Bio-inspired catalysis in water

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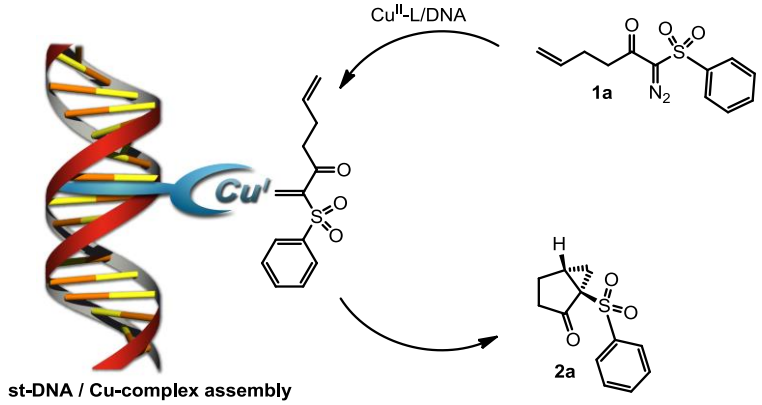
Chapter 2 DNA-based asymmetric organometallic catalysis in water

In this chapter the first example of DNA-based organometallic catalysis giving rise to high *ee*'s will be described. Up to 84% *ee* was achieved in the intramolecular cyclopropanation of α-diazo-β-keto sulfones, catalyzed by Cu^{I}, in the presence of salmon testes DNA as the only source of chirality. The influence of ligand structure on yield and enantioselectivity was investigated and several dipyrido[3,2-a:2',3'-c]phenazine (dppz) derivatives were synthesized. A major side reaction was found, which was studied by mass analysis and NMR spectroscopy to prove that it is the insertion reaction of the carbenoid into the O-H bond of water.



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2.1. Introduction

DNA-based asymmetric catalysis has emerged as a powerful new approach to enantioselective catalysis in water (see chapter 1).[1-6] In this concept, a hybrid catalyst is created by binding a catalytically active metal complex to a DNA scaffold, which allows for the unique chirality of DNA to be translated into enantioselectivity in the catalyzed reaction. This concept has been applied successfully in a variety of catalytic enantioselective reactions such as Diels-Alder,[7] Friedel-Crafts,[3, 8] (oxa-)Michael reactions,[9, 10] fluorinations[11] and the syn-hydration of enones,[12] with good to excellent *ee*'s in all cases. These reactions have in common that they are all Lewis acid catalyzed, employing Cu^{II} as the catalytic metal ion.

2.1.1. Organometallic DNA based catalysis

Indeed, examples not involving Lewis acid catalysis are scarce and, to date, did not result in high enantioselectivities. An allylic amination reaction catalyzed by an Ir^{I} coordinated to a chiral diene ligand that was covalently anchored to the DNA, was reported by Jäschke et al.[13] It was shown that the nature of the oligonucleotide modulates the stereochemical course of the reaction, i.e. which enantiomer is obtained in excess. However, the maximum *ee*'s achieved were low and similar to those obtained with the Ir^{I} complex of the chiral diene ligand alone. Thus, no beneficial effect of the DNA scaffold om the *ee* was observed. In another example, Pd-complexes of phosphine modified mono-nucleotides were also used in allylic substitution reactions with good *ee*'s in THF as solvent. But only low activities and enantioselectivities were obtained with longer oligonucleotides in water.[14]

2.1.2. Carbene reactions

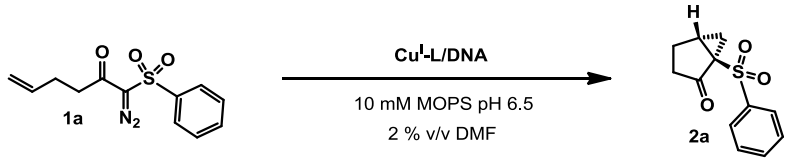
Carbenes are important intermediates in organic synthesis[15] and the catalytic formation of organometallic carbenoids in the presence of transition metals makes them reliable and controllable species for asymmetric catalysis.[16-20] Cyclopropanations are well known reactions of carbenes and especially rhodium[19] and copper[17, 18] complexes are recognized as preferred catalysts in organic solvents. However, due to the low solubilities of transition metal catalysts in water and the high tendency for insertion into the O-H bond of water, it still remains a major challenge to perform asymmetric cyclopropanation in aqueous media.[21, 22] Relatively few examples of metal catalysts that gave rise to high stereo- and/or enantioselectivities in water or aqueous media have been reported and these are based on rhodium[23-26] and ruthenium[27-29] and more recently cobalt[30, 31] and iron.[32, 33]

2.1.3. Intramolecular cyclopropanation of α-diazo-β-keto sulfones.

Nakada et al. published the intramolecular cyclopropanation of **1a** under strictly anhydrous conditions in toluene catalyzed by CuOTf / bisoxazoline complexes.[34] The diazo-compound **1a** is stable at room temperature for several months, but readily forms a metal carbene complex with Cu^{I} at room temperature, which subsequently reacts in an intramolecular cyclopropanation to give **2a**. This transformation was used as the benchmark reaction in the present study. Due to the large structural change occurring during an intramolecular cyclopropanation, we expected this reaction to be sensitive to the chirality of DNA when taking place in close proximity to the DNA double helix.

2.1.4. Research goal

In view of the enormous synthetic potential, the aim of this study was to expand the catalytic scope of DNA-based asymmetric catalysis to include organometallic reactions. Here, the first example of DNA-based organometallic catalysis in water that results in high *ee*'s: the catalytic enantioselective intramolecular cyclopropanation of α-diazo-β-keto sulfones is described (scheme 1).



Scheme 1 Intramolecular cyclopropanation of **1a** in water using a DNA-based catalyst

2.2. Results and Discussion

2.2.1. Experimental setup

The catalytic reactions were performed in 10 mM 3-(N-morpholino)propanesulfonic acid (MOPS) buffer pH 6.5 at room temperature. For formation of the copper-carbenoid with **1a,** the catalyst needs to be in the Cu^I oxidation state. However, the use of Cu^I complexes under these conditions resulted in partial precipitation of the catalyst. Therefore, in our initial studies, 2 mM of sodium ascorbate was added to reduce the Cu^{II} to Cu^I *in situ*. Then it was found that when **1a** was treated with 0.15 mM (15 mol%) of $Cu(NO_3)_2$ without reducing agent present, in deoxygenated buffer inside a glove box to prevent back oxidation to Cu^{II},[35] the reaction also proceeded to give full conversion of **1a** after 3 days (table 1 entry 2).[36] Since higher enantioselectivities were obtained in the catalyzed reaction without sodium ascorbate present, (vide infra), these conditions were selected for this study.

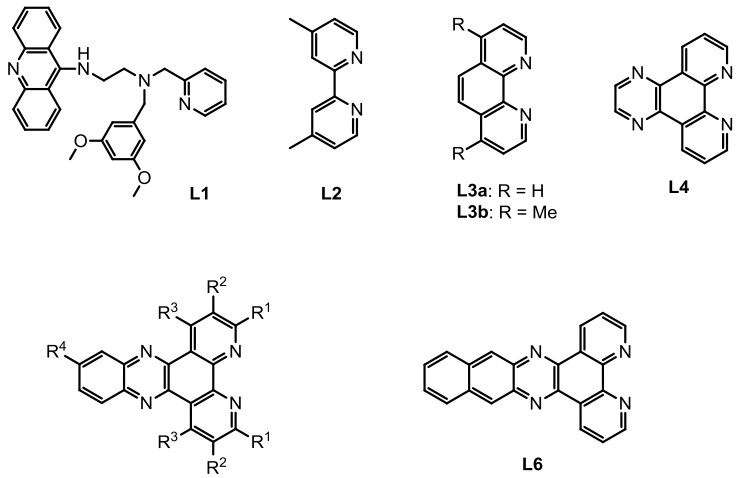


Figure 1 Ligands used in this study.

Table 1 Cu/DNA-catalyzed intramolecular cyclopropanation of **1a**

Entry	$[Cu(NO_3)_2]$ (mol %)	Ligand	[Ligand] (mol %)	Conversion [%][b]	Yield[b] [%]	*ee*[b] [%]
Ligand to copper ratio 1:1[c]						
1[e]	15	**-**	-	45	17	0
2[f]	15	**-**	-	full	76	0
3	15	**-**	-	38	0	0
4[g]	15	**L1**	15	42	0	0
5	15	**L2**	15	45	0	0
6	15	**L3a**	15	48	5	10
7	15	**L4**	15	63	10	28
8	15	**L5a**	15	73	19	37
9[h]	15	**L5a**	15	82	11	29
10	30	**L5a**	30	64	20	59
11[f]	15	**L5a**	15	full	76	0
12	15	**L5b**	15	35	17	26
13	15	**L5c**	15	56	<5	<5
14	15	**L5d**	15	83	17	12
15	15	**L5e**	15	60	13	60
16	30	**L5e**	30	81	26	73
17[g]	15	**L6**	15	41	<5	<5
Ligand to copper ratio 2:1[d]						
18[i]	30	**L5a/ L2**	30/30	80	20	61
19[j]	30	**L5a/ L3b**	30/30	full	28	76
20[g]	30	**L5a**	60	62	19	67
21[g]	30	**L5e**	60	62	30	84
22[g,j]	30	**L5e**	60	full	46	83

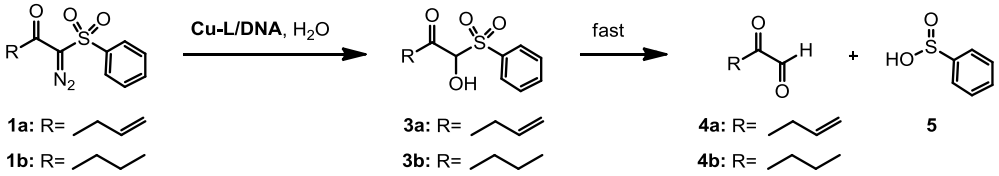
[a] The experiments were carried out in the glove box, with 1 mM **1a**, 1.5 mM base pairs of st-DNA and the indicated concentration of Cu-complex in deoxygenated 10 mM MOPS buffer (pH 6.5), 2% v/v DMF, for 3 days at room temperature, unless otherwise specified. [b] Conversions, yields and enantioselectivities are based on areas of HPLC peaks that are compared to methyl phenyl sulfone as external standard. All data were averaged over two experiments. Product **2a** was obtained in (1*R*, 5*R*)-configuration by comparison of the elution order with those reported previously.[38] [c] Reproducibility: *ee*'s and yields ±5%, conversions ±10%. [d] Reproducibility: *ee*'s ±3%, yields ±5%, conversions ±10%. [e] non-deoxygenated solution without DNA. [f] without DNA. [g] Complex pre-formed in DMF prior to the reaction. [h] with 2 mM sodium ascorbate. [i] 30 mol% (0.30 mM) of isolated Cu-**L5a**, 0.30 mM of ligand **L2** or **L3b** added after incubation of Cu-**L5a** complex with st-DNA for 3 hours. [j] 6 days reaction time.

Self-assembly of the DNA-based catalyst was achieved by addition of a deoxygenated solution of commercially available salmon testes DNA (st-DNA) to a Cu^{II} complex in deoxygenated buffer. The formation of the cyclopropanation product was not obtained with $Cu(NO_3)_2$ alone in presence of st-DNA (entry 3). Copper complexes of ligands **L1** and **L2** (figure 1) in combination with st-DNA, which afforded the highest *ee*'s in the DNA-based catalytic reactions reported previously[7-10], gave rise to a moderate conversion of **1a**, but no significant amount of cyclopropanation product was formed (entry 4, 5). Using catalysts

based on ligands **L3-L5a** that have a larger aromatic area**,** the cyclopropanation product **2a** was obtained in a yield of up to 19 % (entry 8). The addition of 2 mM of sodium ascorbate to force the reduction of Cu^{II}-**L5a**, gave rise to an increase in conversion but a decrease in yield (entry 9).

2.2.2. Side reaction

The observations mentioned above suggest the presence of a competing side reaction, which was expected to be the insertion reaction into the O-H bond of water,[37] a common reaction of metal-carbene complexes in aqueous solutions.[38-40] However, in the course of our study, the OH-bond insertion product **3a** was not detected in significant amounts in the crude product. Zwanenburg et al. reported that α-hydroxy sulfones,[41] which in this case are the products of O-H insertion, are rapidly decomposed in water, yielding the aldehyde **4a** and phenyl sulfinic acid **5** (scheme 2).[42]



Scheme 2 O-H bond insertion with Cu-L/DNA in water and subsequent decomposition. For **1b**: catalytic reaction with 1 mM **1b** and 0.15 mM Cu-**L5a** in water.

This hypothesis was tested by treating the model substrate **1b**, which cannot undergo cyclopropanation, with Cu-**L5a** in water. The ^{1}H-NMR of the lyophilized aqueous phase of the catalytic reaction only showed aromatic peaks corresponding to signals expected for phenyl sulfinic acid **5** or phenyl sulfonic acid, which would be the product resulting from oxidation of **5** (figure 2). Additional mass analysis of the organic phase showed, among others, peaks at m/z = 115 and 141 indicated the presence of **4b** and **5** (figure 3). These results strongly suggest that indeed O-H insertion reaction with water, leading to the formation of **3a**, is the main side reaction occurring during the catalysis.

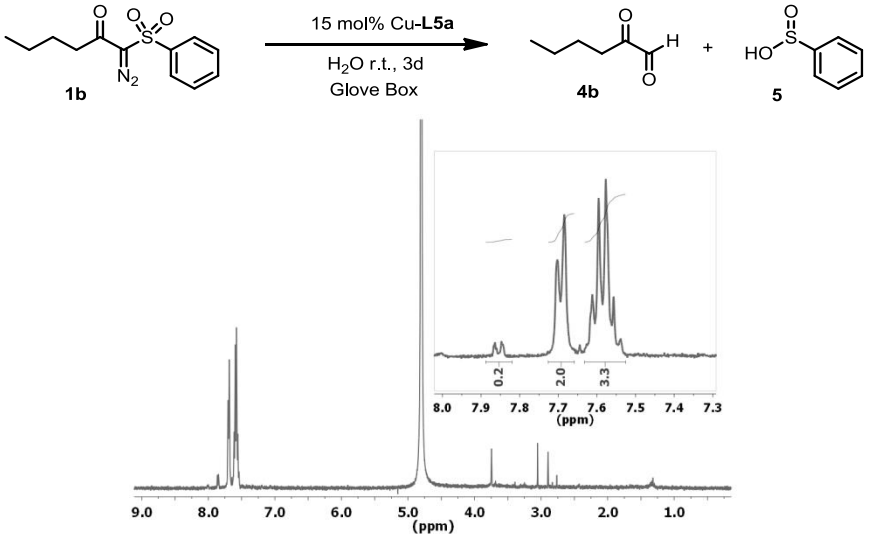


Figure 2 ^{1}H-NMR of the aqueous phase in d_6-DMSO.

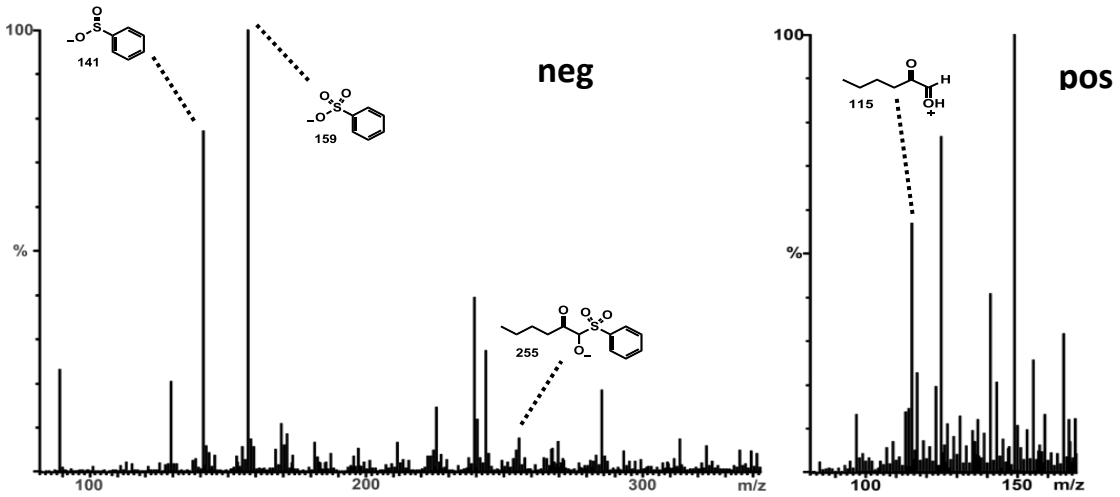


Figure 3 Mass analysis of the organic phase by DART (Direct Analysis in Real time) ionization technique (negative and positive mode).

Interestingly, with st-DNA and copper complex of ligand **L3a** for the first time enantioselectivity was observed (entry 6). The *ee* was found to increase when the aromatic system of the ligand became larger: up to 37 % *ee* of the (1*R*, 5*R*) enantiomer[34] was reached for product **2a** using dipyrido[3,2-a:2',3'-c]phenazine (dppz, **L5a**), which is a known intercalator for DNA (entry 8).[43, 44] As described above the addition of 2 mM of sodium ascorbate decreased the yield of the reaction. Furthermore, the enantioselectivity was also found to be lower (entry 9). Surprisingly, with the copper complex of ligand **L6** bearing an additional phenyl ring no product formation was observed (entry 17).

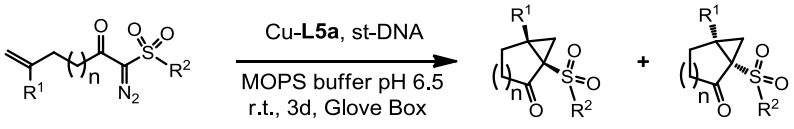
2.2.3. Dppz derivatives

In the light of these results, the dppz ligand was used as starting point for further optimization. Based on our previous experience that showed the beneficial effect of methyl substituents on bipyridine-type ligands in catalysis,[7, 9] ligands **L5b-e** carrying methyl substituents at various positions on the dppz core were synthesized[45-47] and evaluated in the catalytic cyclopropanation. Using ligands **L5b** and **L5d**, **2a** was obtained in similar yields but with lower *ee*'s, whereas with **L5c** no cyclization product was formed (entry 12 - 14). Surprisingly, with **L5e** that contains two methyl substituents located para to the nitrogens of the pyridine rings, the *ee* improved markedly to 60% (entry 15).

Addition of a second equivalent of ligand **L5a** to Cu-**L5a**-DNA led to a small increase of *ee* (entry 20). Since it has been observed before that sometimes hetero combinations of ligands can give rise to higher *ee*'s in asymmetric catalysis[48-50], also combinations of **L2** and **L3b** with pre-incubated Cu-**L5a**-DNA were evaluated. Indeed, it was observed that the enantioselectivity was increased to 76% in case of **L3b** (entry 19). However, the best enantioselectivity, that is 84%, was obtained using two equivalents of ligand **L5e** with respect to copper (entry 21). This value represents the highest enantiomeric excess reported for product **2a** to date.

2.2.4. Substrate scope

The substrate scope of the DNA-hybrid catalyzed asymmetric cyclopropanation was evaluated with a variety of different α-diazo sulfones **1c-g** (scheme 3). With substrates **1c** and **1d** conversion was observed, but no cyclopropanation product was obtained. Apparently, the formation of the five membered ring **2c** with an *o*-tolyl group next to the sulfone and the formation of the six membered ring product **2d** were too slow and thus could not compete with the O-H bond insertion reaction. Substrate **1e** containing a methyl substituent at the internal position of the double bond did also not react under standard catalysis conditions (table 2, entry 3). However, in contrast to **1c** and **1d**, addition of sodium ascorbate as reducing agent to force the formation of the Cu^{I} species did result in cyclopropanation of **1e** giving 40% yield of **2e**. However, the enantioselectivity was low (table 2, entry 4). In case of substrates **1f** and **1g** a low yield of the cyclopropanation products was obtained and the observed enantioselectivities were moderate (table 2, entry 5, 6).



1c, **2c**: n = 1; R^1= H, R^2= *o*-tolyl
1d, **2d**: n = 2; R^1= H, R^2= phenyl
1e, **2e**: n = 1; R^1= Me, R^2= phenyl
1f, **2f**: n = 1; R^1= H, R^2= 2-pyridyl
1g, **2g**: n = 1; R^1= H, R^2= *p*-tolyl

Scheme 3 Substrate scope investigations of Cu/DNA catalyzed asymmetric cyclopropanations.

Table 2 Results of the substrate scope investigations.[a]

Entry	Substrate	Conversion[b] [%]	Yield[b] [%]	*ee*[b] [%]
1	**1c**	78	0	n.d.
2	**1d**	26	0	n.d.
3[c]	**1e**	n.d.	2	n.d.
4[c,d]	**1e**	n.d.	40	16
5[c]	**1f**	n.d.	13	51
6[c]	**1g**	n.d.	29	63 (1*R*, 5*R*)

[a] The experiments were carried out in the glove box, with 1 mM **1a**, 1.5 mM base pairs of st-DNA, 30 mol% (0.30 mM) of $Cu(NO_3)_2$ and 0.30 mM of **L5a** mixed in DMF prior to the reaction, in 10 mM of deoxygenated MOPS buffer (pH 6.5), 2% v/v DMF, for 3 days at room temperature, unless otherwise specified. n.d. = not determined. [b] Conversions, yields and enantioselectivities are based on areas of HPLC peaks that are compared to methyl phenyl sulfone as external standard. All data are averaged over two experiments. Reproducibility: *ee*'s and yields ±5%, conversions ±10%. [c] 30 mol% (0.30 mM) of $Cu(NO_3)_2$ and 0.60 mM of **L5e** mixed in DMF prior to the reaction. [d] with 2 mM sodium ascorbate.

2.2.5. General observations

From the results above, a few notable observations can be made with regard to catalyst design and in particular the choice of the ligand for copper. First of all, a strongly intercalating ligand such as dppz or its derivatives is necessary in the DNA-based catalytic reaction to achieve formation of the cyclopropanation product. Most likely, the dppz-based catalyst accelerates the cyclopropanation to such an extent that it can compete with the O-H bond insertion reaction. Additionally, dppz derivatives were also the ligands with which the highest *ee*'s were achieved in the catalyzed reaction. These observations are in marked contrast with the previously reported DNA-based Cu^{II} catalyzed C-C bond forming reactions in which the complex of weakly binding ligands that are not pure intercalators, such as bipyridines, always gave rise to higher activities and selectivities. A tentative explanation for this observed difference is that in the present case, the kinetically stable and structurally rigid stacking of the intercalating ligands of the copper complex between the base-pairs of the DNA results in a microenvironment that limits access of surrounding water to the catalytic site, i.e. the Cu^{I}-carbene complex. Thus cyclopropanation is favored compared to O-H insertion. Moreover, the close proximity of the catalyzed reaction to the chiral DNA helix results in an efficient transfer of chirality and, as a result, high enantioselectivity in the product.

Secondly, in line with previous observations, it was found that methyl substituents on selected positions of the ligand resulted in higher enantioselectivities in the catalyzed reaction. Strikingly, the relative positions of these methyl substituents are the same as in ligand **L2**, which similarly gave significantly higher *ee*'s compared to unsubstituted 2,2'-bipyridine in DNA-based Lewis acid catalyzed reactions.[51] The reason for the importance of methyl groups at this position, which is remote from where the catalysis occurs is intriguing but at present not understood. Finally, the highest *ee*'s were obtained using ligand to copper ratios of 2:1. No, or only a negligible, increase of enantioselectivity was reported before for Cu^{I} catalyzed insertion reaction with ligand to copper ratios of 2:1.[52, 53]

2.3. Conclusion

Here, the first examples of DNA-based asymmetric organometallic catalysis in water resulting in high ee's have been shown. Up to 84 % *ee* was achieved in the intramolecular cyclopropanation of α-diazo-β-keto sulfones. Additionally, this study represents, to the best of our knowledge, the first copper catalyzed asymmetric cyclopropanation in water.[54] Even though O-H bond insertion is a major side reaction for copper-carbenes in water, these results do demonstrate for the first time that enantioselective organometallic catalysis is feasible using the DNA-based asymmetric catalysis concept. Thus, this study unequivocally demonstrates that DNA-based catalysis can be expanded beyond Lewis acid catalyzed reactions and provides a promising basis for further explorations of DNA-metal-hybrid catalysts for synthetically important transformations in water.

2.4. Experimental Section

2.4.1. General Remarks

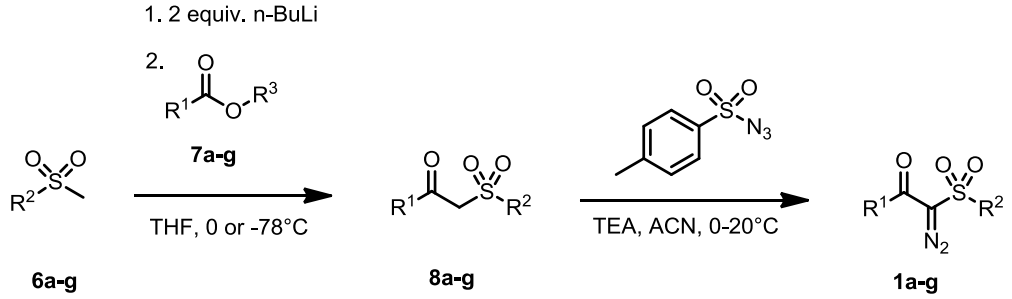
Salmon testes DNA, compounds **L2, L3, 6** and **7** were obtained from Sigma Aldrich and used without further purifications. Sulfone **6f**[55], *β*-keto sulfones **8a,c,g**[34, 56], ligands **L4, L5a-c** and **L6**[45-47] and copper complexes of ligand **L2** and **L3,**[7] **L4** and **L5**[44] were synthesized following published procedures. ^{1}H-NMR, and ^{13}C-NMR spectra were recorded on a Varian 400 (400 and 100 MHz). Chemical shifts (δ) are denoted in ppm using residual solvent peaks as internal standard (δ_H=7.26 and δ_C=77.0 for $CDCl_3$). For all diazo compounds no ^{13}C signal of the carbon bound to the diazo function was observed, which is in agreement with literature.[34] High resolution mass spectra (HRMS) were recorded on an Orbitrap XL (Thermo Fisher Scientific; ESI pos. mode). Enantiomeric excess determinations were performed by HPLC analysis (Chiralpak-ADH or Chiralpak-ASH) using UV-detection (Shimadzu SCL-10Avp). Flash chromatography was performed using silica gel 60 Å (Merck, 200-400 mesh) or a Grace Reveleris® Flash System (40 µm silica column).

2.4.2. Representative procedure

Representative procedure for the asymmetric cyclopropanation of 1 catalyzed by DNA/Cu-complex

Salmon testes DNA (1.5 mg/ml) was dissolved in 10 mM solution of MOPS buffer pH 6.5 (2.25 mM in base pairs) 24 hours before use. The DNA solution and buffer were deoxygenated by bubbling a stream of nitrogen through the solution for at least 4 hours and then was transferred into a glove box (O_2 <20ppm). To reach a final concentration of 1.0 mM of substrate **1**, 0.3 mM of copper complex and 1.5 mM of DNA base pairs; 100 µl of a 22.5 mM solution of previously formed copper complex in DMF was added to 2.350 ml of buffer in a 15 ml plastic tube. Then, 5 ml of st-DNA solution was slowly added and the solution was mixed by continuous inversion at room temperature. After incubation for 16 hours, 50 µl of a 150 mM solution of **1** in DMF was added to start the catalytic reaction. After 3 days the product was extracted with EtOAc (3 x 7.5 mL). After drying (Na_2SO_4) and evaporation of the solvent the crude product was analyzed by HPLC, using methyl phenyl sulfone as external standard.

2.4.3. Synthesis protocols and analytic data



6a, R^2= phenyl — **7a**: R^1= — R^3= CH_3 — **8a**, **1a**: R^1= — R^2= phenyl

6b, R^2= phenyl — **7b**: R^1= — R^3= CH_3 — **8b**, **1b**: R^1= — R^2= phenyl

6c, R^2= *o*-tolyl — **7c**: R^1= — R^3= CH_3 — **8c**, **1c**: R^1= — R^2= *o*-tolyl

6d, R^2= phenyl — **7d**: R^1= — R^3= CH_3 — **8d**, **1d**: R^1= — R^2= phenyl

6e, R^2= phenyl — **7e**: R^1= — R^3= CH_2CH_3 — **8e**, **1e**: R^1= — R^2= phenyl

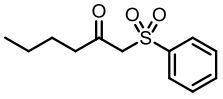
6f, R^2= pyridyl — **7f**: R^1= — R^3= CH_3 — **8f**, **1f**: R^1= — R^2= pyridyl

6g, R^2= *p*-tolyl — **7g**: R^1= — R^3= CH_3 — **8g**, **1g**: R^1= — R^2= *p*-tolyl

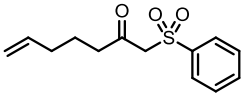
Scheme 4 General synthesis of diazo substrates **1a-g**

General procedure 1: Synthesis of *β*-keto-sulfones **8**:

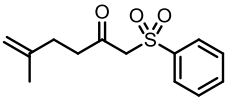
Under inert atmosphere sulfone **6** (5 mmol) was dissolved in dry THF (50 ml). n-Butyllithium in hexane (1.6 M, 10 mmol, 6.25 ml) was added dropwise at 0 °C and the mixture was stirred for additional 10 min. To this strong yellow suspension, ester **7** (6.0 mmol) in 2 ml THF was added in two portions. The mixture discolored and was stirred at 0 °C for 30 min. The reaction was quenched with saturated aqueous NH_4Cl solution (50 ml) and extracted with Et_2O (50ml) and CH_2Cl_2 (2 x 50 ml). The combined organic layers were washed with brine (50ml), dried over Na_2SO_4 and the solvent was evaporated.



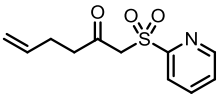
1-(phenylsulfonyl)hexan-2-one (8b).
Synthesized using general procedure 1 starting from (1.562 g, 10 mmol) **6a**. Purified by column chromatography (SiO_2, 20% EtOAc:heptane), to afford the product as a white solid. Yield: 1.38 g (5.74 mmol, 57%) of **8b**. mp = 75 – 76 °C.^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.91 – 7.81 (m, 2H), 7.67 (t, *J*=6.8, 1H), 7.56 (dd, *J*=7.9, 7.9, 2H), 4.14 (s, 2H), 2.68 (t, *J*=7.2, 2H), 1.58 – 1.44 (m, 2H), 1.28 (tq, *J*=7.3, 7.3, 2H), 0.88 (t, *J*=7.3, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 198.2, 138.7, 134.2, 129.3, 128.2, 66.7, 44.1, 25.1, 21.9, 13.7. HRMS calcd for $C_{12}H_{17}O_3S^+$ $[M+H]^+$: 241.089, found 241.089.



1-(phenylsulfonyl)hexan-2-one (8d).
Synthesized using general procedure 1 starting from (500 mg, 3.2 mmol) **6a**. Purified by column chromatography (SiO_2, 20% EtOAc:heptane), to afford the product as a white solid. Yield: 478 mg (1.89 mmol, 59%) of **8d.** mp = 32 – 34 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.92 – 7.83 (m, 2H), 7.69 (t, *J*=7.5, 1H), 7.58 (dd, *J*=7.9, 7.9, 2H), 5.84 – 5.64 (m, 1H), 5.09 – 4.90 (m, 2H), 4.14 (s, 2H), 2.71 (t, *J*=7.2, 2H), 2.14 – 1.94 (m, 2H), 1.70-1.64 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 198.0, 138.7, 137.5, 134.3, 129.3, 128.3, 115.6, 66.9, 43.6, 32.6, 22.2. HRMS calcd for $C_{13}H_{17}O_3S^+$ $[M+H]^+$: 253.090, found 253.089.



5-methyl-1-(phenylsulfonyl)hex-5-en-2-one (8e).
Synthesized using general procedure 1 starting from (915 mg, 5.86 mmol) **6a**. Purified by column chromatography (SiO_2, 20% EtOAc:heptane), to afford the product as a colorless oil. Yield: 992 mg (3.93 mmol, 67%) of **8e** ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.88 (d, *J*=7.4, 2H), 7.68 (t, *J*=7.5, 1H), 7.57 (dd, *J*=7.9, 7.9, 2H), 4.75 – 4.72 (m, 1H), 4.66 – 4.63 (m, 1H) 4.16 (s, 2H), 2.85 (t, J=7.4, 2H), 2.26 (t, J=7.4, 2H), 1.71 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 197.5 143.5, 138.6, 134.2, 129.3, 128.2, 110.7, 66.8, 42.5, 30.8, 22.5. HRMS calcd for $C_{13}H_{17}O_3S^+$ $[M+H]^+$: 253.090, found 253.089.



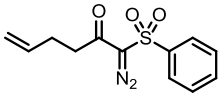
1-(pyridin-2-ylsulfonyl)hex-5-en-2-one (8f).
6f (0,786 g, 5 mmol) was dissolved in 50 ml dry THF and cooled to -78°C. n-Butyllithium (6.25 ml, 1.6 mM solution in hexane, 10.00 mmol) was added dropwise at -78°C, over 20 min and stirred for another 20 min. To this solution **7f** (0.599 g, 5.25 mmol) in 1.5 ml THF was added dropwise at -78°C over 20 min and stirred for another 20 min. Then the reaction mixture was allowed to warm to room temperature over 30 min and was quenched with saturated aqueous NH_4Cl solution (50 ml). The aqueous phase was extracted with ether (3 x 30 ml) and the combined organic layers were washed with brine (50 ml), dried over Na_2SO_4 and evaporated. The residue was purified by column chromatography (SiO_2, 50% EtOAc:heptane) to afford the product as an orange oil. Yield: 778 mg (3.25 mmol, 65%) of **8f**. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.72 (d, *J*=4.7, 1H), 8.05 (d, *J*=7.8, 1H), 7.97 (td, *J*=7.7, 1.6, 1H), 7.57 (ddd, *J*=7.5, 4.7, 0.8, 1H), 5.74 (ddt, *J*=16.8, 10.2, 6.5, 1H), 5.06 – 4.89 (m, 2H), 4.48 (s, 2H), 2.79 (t, *J*=7.2, 2H), 2.30 (t, *J*=7.0, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 197.4, 156.6, 150.1, 138.3, 136.0, 127.7, 122.1, 115.76, 62.3, 43.3, 27.0. HRMS calcd for $C_{11}H_{14}NO_3S^+$ $[M+H]^+$: 240.069, found 240.069.

General procedure 2: Synthesis of diazo compounds **1**:

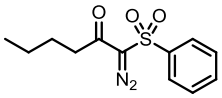
Under inert atmosphere *β*-keto sulfone **8** (3.0 mmol) was dissolved in CH_3CN (25 ml) and triethylamine (450 mg, 4.50 mmol) was added at 0°C. Then freshly prepared 4-methylbenzenesulfonyl azide (592 mg, 3,60 mmol) was added dropwise while stirring. The reaction mixture was allowed to warm to room temperature while stirring for 3 h. Then the mixture was washed with saturated NH_4Cl (10 ml) and the aqueous layer was extracted with ether (3 x 10 ml). The combined organic phases were washed with 10% KOH (5 ml), saturated $NaHCO_3$ (5 ml), and saturated NaCl (5 ml), dried over anhydrous $MgSO_4$ and

concentrated in vacuo at room temperature until ~1ml solvent was left. The product was purified by for column chromatography.

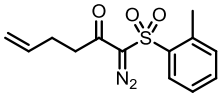
Note: For all diazo compounds no ^{13}C signal of the carbon bound to the diazo function was observed, which is in agreement with literature.[34]



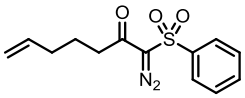
1-diazo-1-(phenylsulfonyl)hex-5-en-2-one (1a).
Synthesized using general procedure 2 starting from (2 g, 8.39 mmol) **8a**. Purified by column chromatography (SiO_2, 10% EtOAc:heptane), to afford the product as a yellow solid. Yield: 2.04 g (7.33 mmol, 87%) of **1a**. mp = 38 – 40 °C. ^1H NMR (400 MHz, $CDCl_3$) δ = 7.97 (d, *J*=7.3, 2H), 7.67 (t, *J*=7.4, 1H), 7.58 (dd, *J*=7.4, 7.3, 2H), 5.81 – 5.58 (m, 1H), 5.03 – 4.84 (m, 2H), 2.64 (t, *J*=7.3, 2H), 2.33 – 2.21 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 187.6, 142.0, 135.9, 134.2, 129.5, 127.2, 115.9, 38.2, 27.5. HRMS calcd for $C_{12}H_{13}N_2O_3S^+$ $[M+H]^+$: 265.064, found 265.064.



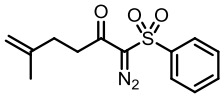
1-diazo-1-(phenylsulfonyl)hexan-2-one (1b).
Synthesized using general procedure 2 starting from (481mg, 2.00 mmol) **8b**. Purified by column chromatography (SiO_2, 10% EtOAc:heptane), to afford the product as a yellow oil. Yield: 394 mg (1.48 mmol, 74%) of **1b.** mp = 34 – 35 °C. ^1H NMR (400 MHz, $CDCl_3$) δ = 7.96 (dd, *J*=5.3, 3.4, 2H), 7.65 (ddd, *J*=6.7, 3.9, 1.2, 1H), 7.56 (dd, *J*=10.5, 4.8, 2H), 2.52 (t, *J*=7.4, 2H), 1.55 – 1.46 (m, 2H), 1.30 – 1.19 (m, 2H), 0.82 (t, *J*=7.3, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 188.4, 142.0, 134.1, 129.4, 127.2, 38.8, 25.6, 212.0, 13.6. HRMS calcd for $C_{12}H_{15}N_2O_3S^+$ $[M+H]^+$: 267.080, found 267.080.



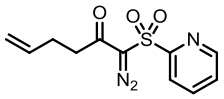
1-diazo-1-(phenylsulfonyl)hex-5-en-2-one (1c).
Synthesized using general procedure 2 starting from (675 mg, 2.68 mmol) **8c**. Purified by column chromatography (SiO_2, 10% EtOAc:heptane), to afford the product as a yellow solid. Yield: 564 mg (2.03 mmol, 76%) of **1c**. mp = 40 – 41 °C. ^1H NMR (400 MHz, $CDCl_3$) δ = 8.12 (d, *J*=8.0, 1H), 7.55 (t, *J*=7.5, 1H), 7.46 – 7.33 (m, 2H), 5.62 (m, 1H), 4.97 – 4.82 (m, 2H), 2.61 (s, 3H), 2.54 (t, *J*=7.3, 2H), 2.23 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 188.0, 139.5, 137.4, 135.9, 134.2, 133.1, 130.2, 126.7, 115.7, 38.1, 27.5, 20.1. HRMS calcd for $C_{13}H_{14}N_2O_3SNa^+$ $[M+Na]^+$: 301.062, found 301.062



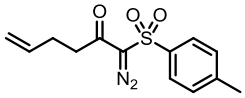
1-diazo-1-(phenylsulfonyl)hex-5-en-2-one (1d).
Synthesized using general procedure 2 starting from (400 mg, 1.59 mmol) **8d**. Purified by column chromatography (SiO_2, 10% EtOAc:heptane), to afford the product as a yellow oil. Yield: 231 mg (0.83 mmol, 53%) of **1b**. ^1H NMR (400 MHz, $CDCl_3$) δ = 8.04 – 7.91 (m, 2H), 7.67 (dd, *J*=10.6, 4.3, 1H), 7.58 (dd, *J*=10.5, 4.8, 2H), 5.75 – 5.57 (m, 1H), 5.00 – 4.88 (m, 2H), 2.54 (t, *J*=7.3, 2H), 2.01 (m, 2H), 1.67 (dd, *J*=14.6, 7.3, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 188.5, 142.3, 137.6, 134.4, 129.7, 127.6, 115.8, 38.5, 32.9, 22.8. HRMS calcd for $C_{13}H_{15}N_2O_3S^+$ [M+H]: 279.080 found 279.080.



1-diazo-5-methyl-1-(phenylsulfonyl)hex-5-en-2-one (1e).
Synthesized using general procedure 2 starting from (505 mg, 2.00 mmol) **8e**. Purified by column chromatography (SiO_2, 10% EtOAc:heptane), to afford the product as a yellow oil. Yield: 440 mg (1.58 mmol, 79%) of **1f**. 1H NMR (400 MHz, $CDCl_3$) δ = 8.00 – 7.94 (m, 2H), 7.70 – 7.63 (m, 1H), 7.62 – 7.55 (m, 2H), 4.70 – 4.67 (m, 1H), 4.56 – 4.53 (m, 1H). 2.73 – 2.63 (m, 2H), 2.24 (t, J=7.6, 2H), 1.65 (s, 3H).13C NMR (101 MHz, $CDCl_3$) δ = 187.8, 143.4, 142.0, 134.1, 129.5, 127.3, 110.6, 37.3, 31.1, 22.5. HRMS calcd for $C_{13}H_{14}N_2O_3SNa^+$ $[M+Na]^+$: 301.062, found 301.062.



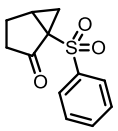
1-diazo-1-(pyridin-2-ylsulfonyl)hex-5-en-2-one (1f).
Synthesized using general procedure 2 starting from (400mg, 1.67 mmol) **8f**. Purified by column chromatography (SiO_2, 20% EtOAc:heptane), to afford the product as a yellow oil. Yield: 201 mg (0.76 mmol, 48%) of **1d.** ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.75-8.69 (m, 1H), 8.10 (dd, *J*=7.9, 1.0, 1H), 7.99 (dd, *J*=7.8, 1.7, 1H), 7.58 (ddd, *J*=7.6, 4.7, 1.1, 1H), 5.74 (dd, *J*=17.0, 10.3, 1H), 5.04 – 4.88 (m, 2H), 2.80 (t, *J*=7.3, 2H), 2.33 (dt, *J*=13.7, 6.9, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 188.6, 159.0, 150.7, 138.6, 136.5, 128.0, 121.8, 115.9, 38.6, 27.9. HRMS calcd for $C_{11}H_{12}N_3O_3S^+$ $[M+H]^+$: 266.060, found 266.060.



1-diazo-1-tosylhex-5-en-2-one (1g).
Synthesized using general procedure 2 starting from (600mg, 2.38 mmol) **8g**. Purified by column chromatography (SiO_2, 10% EtOAc:heptane), to afford the product as a yellow oil. Yield: 431 mg (1.55 mmol, 69%) of **1e**. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.85 (d, *J*=8.4, 2H), 7.37 (d, *J*=8.0, 2H), 5.78-5.68 (m, 1H), 5.06 – 4.86 (m, 2H), 2.65 (t, *J*=7.4, 2H), 2.46 (s, 3H), 2.39 – 2.19 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 188.0, 145.6, 139.4, 136.3, 130.3, 127.6, 116.1, 38.5, 27.8, 21.9. HRMS calcd for $C_{13}H_{14}N_2O_3SNa^+$ $[M+Na]^+$: 301.062, found 301.062.

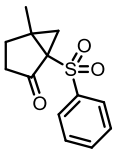
General procedure 3: Synthesis of racemic cyclopropanation products **2**:

Under inert atmosphere diazo compound **1** (0.4 mmol) was dissolved in dry CH_2Cl_2 (8 ml) to give a yellow solution. $Rh_2(OAc)_4$ (2 mol%, 8.00 µmol) was added and the reaction monitored by TLC. After full conversion (~1 h) the solution was filtered over a small batch of SiO_2 to remove the rhodium catalyst. The column was washed with CH_2Cl_2 (8 ml) and the solvent evaporated under reduced pressure to afford the crude product.

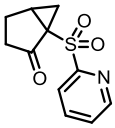


1-(phenylsulfonyl)bicyclo[3.1.0]hexan-2-one (2a).
Synthesized using general procedure 3. starting from (100 mg, 0.378 mmol) **1a**. Purified by flash chromatography (SiO_2, gradient EtOAc:pentane), to afford the product as a white solid. Yield: 51 mg (0.216 mmol, 57%) of **2a**. mp=98-99°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.02 (d, *J*=7.9, 2H), 7.69 – 7.58 (m, 1H), 7.58 – 7.44 (m, 2H), 3.02 (m, 1H), 2.32 – 2.11 (m, 4H), 2.06 – 1.93 (m, 1H), 1.52 (dd, *J*=5.5, 3.7, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 203.4, 139.5, 133.8, 128.9, 128.8, 53.2, 33.7, 31.1, 20.5, 20.3 HRMS calcd for $C_{12}H_{13}O_3S^+$ $[M+H]^+$: 237.058, found 237.058. Enantiomeric excess was determined

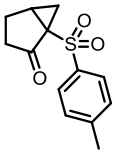
by HPLC analysis (Chiralpak-ADH, n-heptane/iPrOH 90:10, 0.5 ml/min. Retention times: 33.7 and 37.7 min.)



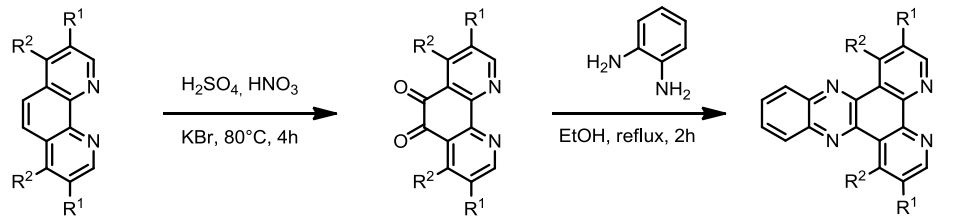
5-methyl-1-(phenylsulfonyl)bicyclo[3.1.0]hexan-2-one (2e).
Synthesized using general procedure 3 starting from (111 mg, 0.400 mmol) **1e** Purified by flash chromatography (SiO_2, gradient EtOAc:pentane), to afford the product as a white solid. Yield: 78 mg (3.12 mmol, 78%) of **2e**. mp=129-130°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.08 – 7.95 (m, 2H), 7.61 (t, *J*=7.4, 1H), 7.52 (dd, *J*=7.9, 7.3, 2H), 2.28 (d, *J*=5.0, 1H), 2.17 – 1.90 (m, 4H), 1.79 (s, 3H), 1.67 (d, *J*=5.1, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 203.9, 140.3, 133.6, 128.9, 128.7, 56.9, 42.2, 33.0, 28.5, 26.2, 18.4. HRMS calcd for $C_{13}H_{15}O_3S^+$ $[M+H]^+$: 251.074, found 251.074. Enantiomeric excess was determined by HPLC analysis (Chiralpak-ADH, n-heptane/iPrOH 90:10, 0.5 ml/min. Retention times: 29.1 and 36.0 min.)



1-(pyridin-2-ylsulfonyl)bicyclo[3.1.0]hexan-2-one (2f).
Diazo compound **1f** (0.4 mmol) was dissolved in deoxygenated H_2O (40 ml) under inert atmosphere to give a yellow solution. $Cu(NO_3)_2(H_2O)_2$ (25 mol%, 0.1 mmol) was added and the reaction monitored by TLC. After full conversion was reached (~18 h), the reaction mixture was extracted with CH_2Cl_2 (3 x 20 ml), the combined organic phases were washed with brine (20 ml) and dried (Na_2SO_4). Then the solvent was evaporated under reduced pressure to afford the crude product, which was purified by flash chromatography (SiO_2, gradient EtOAc:pentane), to afford the product as a colorless oil. Yield: 61 mg (2.72 mmol, 68%) of **2f**. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.70 – 8.63 (m, 1H), 8.22 (t, *J*=7.9, 1H), 7.96 (td, *J*=7.8, 1.7, 1H), 7.51 (dd, *J*= 7.6, 4.7, 1H), 3.05 (dt, *J*=8.7, 5.4, 1H), 2.45 (dd, *J*=8.6, 5.7, 1H), 2.35 – 2.15 (m, 3H), 2.05 (ddd, *J*=11.5, 8.4, 5.5, 1H), 1.67 (t, *J*=5.7, 1H).^{13}C NMR (101 MHz, $CDCl_3$) δ = 203.6, 157.3, 149.8, 138.0, 127.3, 123.6, 50.6, 33.4, 30.6, 20.3, 20.2. HRMS calcd for $C_{11}H_{12}NO_3S^+$ $[M+H]^+$: 238.053, found 238.054. Enantiomeric excess was determined by HPLC analysis (Chiralpak-ASH, n-heptane/iPrOH 90:10, 0.5 ml/min. Retention times: 50.4 and 54.6 min.)



1-tosylbicyclo[3.1.0]hexan-2-one (2g).
Synthesized using general procedure 3 starting from (111 mg, 0.400 mmol) **1g** Purified by flash chromatography (SiO_2, gradient EtOAc:pentane), to afford the product as a white solid. Yield: 80 mg (3.20 mmol, 80%) of **2g**. mp=123-124°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.92 (d, *J*=8.2, 2H), 7.34 (d, *J*=8.1, 2H), 3.09 – 2.95 (m, 1H), 2.44 (s, 3H), 2.33 – 2.10 (m, 4H), 2.01 (dd, *J*=7.0, 4.6, 1H), 1.51 (t, *J*=5.4, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 203.5, 144.7, 136.4, 129.5, 128.7, 53.2, 33.6, 31.0, 21.6, 20.3, 20.2. HRMS calcd for $C_{13}H_{15}O_3S^+$ $[M+H]^+$: 251.074, found 251.074. Enantiomeric excess was determined by HPLC analysis (Chiralpak-ADH, n-heptane/iPrOH 92:8, 0.5 ml/min. Retention times: 37.6 and 39.8 min.)



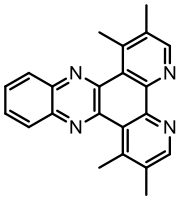
L3b: R^1= H, R^2= Me
L3c: R^1, R^2= Me

L5d: R^1, R^2= Me
L5e: R^1= H, R^2= Me

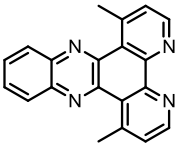
Scheme 5 General synthesis of dppz derivatives **L5d,e**

General procedure 4: Synthesis of dppz derivatives **L5d,e**:

The phenanthroline derivative **L3** (6.5 mmol) and potassium bromide (7.5 g, 63.0 mmol) were combined and stirred. Sulfuric acid (30 ml, 540 mmol) was added dropwise over 15 min at 0°C. After an additional 15 min nitric acid (15 ml, 245 mmol) was added dropwise at 0°C. The resulting mixture was heated at 80°C for 4 h and then cooled to 0°C. The cold acidic mixture was carefully poured out on ice (~300 g). Subsequently, 5% NaOH solution was added slowly under vigorous stirring until the pH reached 3. Then the mixture was extracted with CH_2Cl_2 (3 x 300 ml). The organic phase was dried over $MgSO_4$ and the solvent was evaporated.
Benzene-1,2-diamine (409 mg, 3.78 mmol) was dissolved in ethanol (50 ml). To the stirred solution the crude yellow solid (~1,5 g, 6.3 mmol) was added at room temperature and the mixture was stirred while heating under reflux overnight. Then the ethanol was evaporated and the residue dissolved in 100 ml of CH_2Cl_2. The product was extracted with 0.1 M HCl solution (3 x 100ml). The combined aqueous phases were basified to pH 10 with 1 M NaOH and the precipitate was filtered off and dried. The crude product was purified by recrystallization from CH_2Cl_2.



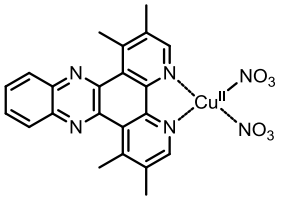
1,2,7,8-tetramethyldipyrido[3,2-a:2',3'-c]phenazine (L5d).
Synthesized using general procedure 4 starting from (1.0 g, 3.93 mmol) 3,4,7,8-tetramethyl-1,10-phenanthroline hydrate. Yield: 376 mg (1.11 mmol, 28%) of **L3c**. mp = decomposition > 250°C, ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.90 (s, 2H), 8.23 (dd, *J*=6.4, 3.4, 2H), 7.83 (dd, *J*=6.4, 3.4, 2H), 3.23 (s, 6H), 2.55 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 152.2, 148.2, 147.1, 144.3, 139.1, 133.5, 129.8, 129.0, 125.0, 20.3, 18.1. HRMS calcd for $C_{22}H_{19}N_4^+$ $[M+H]^+$: 339.160, found 339.160.



1,8-dimethyldipyrido[3,2-a:2',3'-c]phenazine (L5e).
Synthesized using general procedure 4 starting from (1.35 g, 6.5 mmol) 4,7-dimethyl-1,10-phenanthroline. Yield: 129 mg (0.416 mmol, 11%) of **L3b**. mp = decomposition > 265°C, ^{1}H NMR (400 MHz, $CDCl_3$) 9.02 (d, *J*=4.6, 2H), δ = 8.21 (dd, *J*=6.4, 3.4, 2H), 7.82 (dd, *J*=6.5, 3.4, 2H), 7.49 (d, *J*=4.6, 2H), 3.32 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 150.8, 149.8, 149.4, 144.0, 139.6, 130.1, 129.2, 127.9, 125.9, 26.4. HRMS calcd for $C_{20}H_{15}N_4^+$ $[M+H]^+$: 311.129, found 311.129.

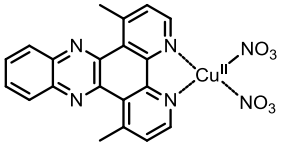
General procedure 5: Synthesis of Copper complexes $Cu(L5)(NO_3)_2$:

$Cu(NO_3)_2 \cdot 3H_2O$ (73.5 mg, 0.30 mmol) and dppz derivative **L5** (0.27 mmol) were dissolved in a minimum amount of ethanol. **L5** was added dropwise to the stirred copper solution and stirring was continued for 1 h at room temperature. The solid was filtered off and washed with ethanol and diethyl ether.



$Cu(L5d)(NO_3)_2$

Synthesized using general procedure 5, starting from (200 mg, 0.591 mmol) **L5d**. Yield: 264 mg (0.485 mmol, 82%) of Cu-**L5d**. Elemental analysis (calcd %) for $C_{22}H_{18}CuN_6O_6 \cdot 1H_2O$: C, 48.57; H, 3.71; N, 15.45; found: C, 49.01; H, 3.31; N, 15.73. ESI-MS positive mode, calcd for $C_{22}H_{18}CuN_5O_3$ $[M\text{-}NO_3]^+$: 463.1, found 463.0.



$Cu(L5e)(NO_3)_2$

Synthesized using general procedure 5, starting from (20 mg, 0.064 mmol) **L5e**. Yield: 24 mg (0.047 mmol, 72%) of Cu-**L5e**. Elemental analysis (calcd %) for $C_{20}H_{14}CuN_6O_6 \cdot 0.5H_2O$: C, 47.39; H, 2.98; N, 16.58; found: C, 47.12; H, 2.71; N, 16.08. ESI-MS positive mode, calcd for $C_{20}H_{14}CuN_5O_3$ $[M\text{-}NO_3]^+$: 435.0, found 435.0.

2.5. References

[1] J. Oelerich, G. Roelfes, *Prog. Inorg. Chem.* **2012**, *47*, 353.

[2] P. J. Deuss, R. den Heeten, W. Laan, P. C. J. Kamer, *Chem. Eur. J.* **2011**, *17*, 4680.

[3] S. Park, H. Sugiyama, *Angew. Chem. Int. Ed.* **2010**, *49*, 3870.

[4] T. Heinisch, T. R. Ward, *Curr. Opin. Chem. Biol.* **2010**, *14*, 184.

[5] S. K. Silverman, *Angew. Chem. Int. Ed.* **2010**, *49*, 7180.

[6] A. J. Boersma, R. P. Megens, B. L. Feringa, G. Roelfes, *Chem. Soc. Rev.* **2010**, *39*, 2083.

[7] G. Roelfes, A. J. Boersma, B. L. Feringa, *Chem. Commun.* **2006**, 635.

[8] A. J. Boersma, B. L. Feringa, G. Roelfes, *Angew. Chem. Int. Ed.* **2009**, *48*, 3346.

[9] D. Coquière, B. L. Feringa, G. Roelfes, *Angew. Chem. Int. Ed.* **2007**, *46*, 9308.

[10] R. P. Megens, G. Roelfes, *Chem. Commun.* **2012**, *48*, 6366.

[11] N. Shibata, H. Yasui, S. Nakamura, T. Toru, *Synlett* **2007**, 1153.

[12] A. J. Boersma, D. Coquière, D. Geerdink, F. Rosati, B. L. Feringa, G. Roelfes, *Nature Chem.* **2010**, *2*, 991.

[13] P. Fournier, R. Fiammengo, A. Jäschke, *Angew. Chem. Int. Ed.* **2009**, *48*, 4426.

[14] L. Ropartz, N. J. Meeuwenoord, G. A. van der Marel, P. W. N. M. van Leeuwen, A. M. Z. Slawin, P. C. J. Kamer, *Chem. Commun.* **2007**, 1556.

[15] H. M. L. Davies, J. R. Denton, *Chem. Soc. Rev.* **2009**, *38*, 3061.

[16] M. Doyle, D. Forbes, *Chem. Rev.* **1998**, *98*, 911.

[17] M. Doyle, M. Protopopova, *Tetrahedron* **1998**, *54*, 7919.

[18] W. Kirmse, *Angew. Chem. Int. Ed.* **2003**, *42*, 1088.

[19] M. Doyle, *Recl. Trav Chim. Pays-Bas* **1991**, *110*, 305.

[20] M. P. Doyle, R. Duffy, M. Ratnikov, L. Zhou, *Chem. Rev.* **2010**, *110*, 704.

[21] H. Pellissier, *Tetrahedron* **2008**, *64, 7041*.

[22] I. Nicolas, P. Le Maux, G. Simonneaux, *Coord. Chem. Rev.* **2008**, *252*, 727.

[23] F. Estevan, J. Lloret, M. Sanau, A. Ubeda, *Organometallics* **2006**, *25, 4977*.

[24] R. Sambasivan, Z. T. Ball, *Angew. Chem. Int. Ed* **2012**, *51*, 8568.

[25] R. Wurz, A. Charette, *Org. Lett.* **2002**, *4*, 4531.

[26] D. C. Wynne, M. M. Olmstead, P. G. Jessop, *J. Am. Chem. Soc.* **2000**, *122*, 7638.

[27] S. Iwasa, F. Takezawa, Y. Tuchiya, H. Nishiyama, *Chem. Commun.* **2001**, 59.

[28] A.-M. Abu-Elfotoh, D. P. T. Nguyen, S. Chanthamath, K. Phemkeona, K. Shibatomi, S. Iwasa, *Adv. Synth. Catal.* **2012**, *354*, 3435.

[29] S. Iwasa, S. Tsushima, K. Nishiyama, Y. Tsuchiya, F. Takezawa, H. Nishiyama, *Tetrahedron-Asymmetry* **2003**, *14*, 855-865.

[30] B. Morandi, B. Mariampillai, E. M. Carreira, *Angew. Chem. Int. Ed.* **2011**, *50*, 1101.

[31] T. Ikeno, A. Nishizuka, M. Sato, T. Yamada, *Synlett* **2001**, 406.

[32] B. Morandi, E. M. Carreira, *Angew. Chem. Int. Ed.* **2010**, *49*, 938.

[33] B. Morandi, A. Dolva, E. M. Carreira, *Org. Lett.* **2012**, *14*, 2162.

[34] M. Honma, T. Sawada, Y. Fujisawa, M. Utsugi, H. Watanabe, A. Umino, T. Matsumura, T. Hagihara, M. Takano, M. Nakada, *J. Am. Chem. Soc.* **2003**, *125*, 2860.

[35] It has been reported that reduction of Cu^{II} pre-catalysts to active Cu^{I} can occur in the presence of diazo compounds. See: R. G. Salomon, J. K. Kochi, *J. Am. Chem. Soc.* **1973**, *95*, 3300.

[36] In non-deoxygenated solutions no reaction was observed with $NiBr_2$, $ZnBr_2$, $AgNO_3$, and $CoCl_2$. A moderate reactivity was found for and $Rh_2(OAc)_4$.

[37] In intermolecular reactions often one of the substrates is added in excess to compensate the loss through O-H bond insertion and to increase the relative yields.

[38] F. Haupter, A. Pucek, *Chem. Ber.* **1960**, *93*, 249.

[39] B. Eistert, P. Donath, *Chem. Ber.* **1969**, *102* 1725.

[40] S. Zhu, C. Chen, Y. Cai, Q. Zhou, *Angew. Chem. Int. Ed.* **2008**, *47*, 932.

[41] α-hydroxy sulfones can, in principle, also be formed by hydrolysis of the diazo compounds.

[42] J. B. F. N. Engberts, B. Zwanenburg, *Tetrahedron* **1968**, *24*, 1737.

[43] B. M. Zeglis, V. C. Pierre, J. K. Barton, *Chem. Commun.* **2007**, 4565.

[44] M. Navarro, E. J. Cisneros-Fajardo, A. Sierralta, M. Fernandez-Mestre, P. Silva, D. Arrieche, E. Marchan, *J. Biol. Inorg. Chem.* **2003**, *8*, 401.

[45] A. Greguric, I. D. Greguric, T. W. Hambley, J. R. Aldrich-Wright, J. G. Collins, *J. Chem. Soc.* **2002**, 849.

[46] D. S. Beaudoin, S. O. Obare, *Tetrahedron Lett.* **2008**, *49*, 6054.

[47] K. L. Reddy, Y. H. K. Reddy, S. Satyanarayana, *Nucleosides, Nucleotides Nucleic Acids* **2009**, *28, 953*.

[48] R. Hoen, J. A. F. Boogers, H. Bernsmann, A. J. Minnaard, A. Meetsma, T. D. Tiemersma-Wegman, A. H. M. de Vries, J. G. de Vries, B. L. Feringa, *Angew. Chem. Int. Ed.* **2005**, *44*, 4209.

[49] M. T. Reetz, T. Sell, A. Meiswinkel, G. Mehler, *Angew. Chem. Int. Ed.* **2003**, *42*, 790.

[50] M. Reetz, *Chim. Oggi*, **2003**, *21*, 5.

[51] A. J. Boersma, J. E. Klijn, B. L. Feringa, G. Roelfes, *J. Am. Chem. Soc.* **2008**, *130*, 11783.

[52] J. M. Fraile, P. López-Ram-de-Viu, J. A. Mayoral, M. Roldán, J. Santafé-Valero, *Org. iomol. Chem.* **2011**, *9*, 6075.

[53] M. P. A. Lyle, N. D. Draper, P. D. Wilson, *Org. Biomol. Chem.* **2006**, *4*, 877.

[54] In one report it was shown that the presence of traces of water had a negative influence on the copper catalyzed cyclopropanation in ionic liquids. See: J. M. Faile, J. I. Carcía, C. I. Herrerías, J. A. Mayoral, S. Gmough, M. Vaultier, *Green Chem.* **2004**, *6*, 93.

[55] P. H. Bos, B. Macia, M. A. Fernandez-Ibanez, A. J. Minnaard, B. L. Feringa, *Org. Biomol. Chem.* **2010**, *8*, 47.

[56] H. Takeda, M. Nakada, *Tetrahedron-Asymmetry* **2006**, *17*, 2896.